# GUIDANCE[1]

# GEMFIBROZIL CAPSULES OR TABLETS

# *IN VIVO* BIOEQUIVALENCE

# AND *IN VITRO* DISSOLUTION TESTING

## I.    INTRODUCTION

A.    Pharmacology

Gemfibrozil is used clinically as a lipid-regulatory agent which lowers the serum triglycerides and produces a variable reduction in total serum cholesterol.  The decrease occurs primarily in the very low-density lipoprotein (VLDL) and less frequently in the low-density lipoprotein (LDL).  In addition, there is elevation in the high-density lipoprotein (HDL) concentration (1-4,12).  Gemfibrozil is used in adult patients with all types of dyslipidaemia (except type 1).  The recommended dosage of gemfibrozil is 600 mg twice daily given 30 minutes before morning and evening meals (5).

The mechanism whereby gemfibrozil lowers plasma triglycerides and increases HDL cholesterol concentration is not well established.  One mechanism by which drug reduces circulating triglyceride concentration may be through the suppression of free

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[1]This statement, prepared by the Division of Bioequivalence in the Office of Generic Drugs, is an informal communication under 21 CFR 10.90(b)(9) that represents the best judgment of the Division at this time.  This statement does not necessarily represent the formal position of the Center for Drug Evaluation and Research, Food and Drug Administration, and does not bind or otherwise obligate the Center for Drug Evaluation and Research, Food and Drug Administration, to the views expressed.  For further information about this guidance, contact the Division of Bioequivalence, Office of Generic Drugs, 7500 Standish Place, Metro Park North, Rockville, MD 20855 (Phone:  301-295-8290; Fax: 301-295-8183).

fatty acid mobilization from adipose tissue (6-8).
Gemfibrozil also stimulates lipoprotein lipase activity
(9).

Gemfibrozil is not recommended for use in patients with
hepatic or severe renal dysfunction, including primary
biliary cirrhosis and preexisting gallbladder disease
(10,11).  The main adverse reactions are dyspepsia and
abdominal pain (12).  Gemfibrozil is metabolized to a
number  of compounds in man.  All the metabolites and
unchanged drug form glucuronide conjugates (13,14)
which are excreted in urine.  The metabolites have no
lipid lowering activity (15).

Gemfibrozil is currently marketed as Lopid (Parke-
Davis), 300 mg capsules and 600 mg tablets (NDA 18-422
approved November 20, 1986).

B.     Chemistry

Gemfibrozil is 5-(2,5-dimethylphenoxy)-2,2-
dimethylpentanoic acid.  The structures of gemfibrozil
and its metabolites are given below:

**GEMFIBROZIL AND ITS METABOLITES**

C.     Pharmacokinetics

Following oral administration of gemfibrozil in man,
absorption is rapid and complete.  Peak plasma
concentrations are attained 1 to 2 hours after
administration of single doses up to 2000 mg or after
repeated doses up to 800 mg twice daily (16).  Plasma
drug concentration is directly proportional to dose and
tends to rise during repeated administration, although

steady state is achieved within 7 to 14 days with twice daily doses.  After the administration of gemfibrozil, 600 mg twice daily, mean peak plasma concentrations are about 10 to 15 mg/L (11,12).  The mean elimination half-life of gemfibrozil is 6.5 to 8.0 hours.

## II. BIOEQUIVALENCE STUDIES

A.    Types of studies Required

1.    A single-dose, fasting, two-way crossover study with 2 x 300 mg capsules or 1 x 600 mg tablet gemfibrozil test product compared to the reference product Lopid 2 x 300 mg capsule or 1 x 600 mg tablet.

2.    In vitro dissolution testing for the 300 mg capsules and 600 mg tablets.

B.    Fasting Study

*Objective*:  The objective of this study is to compare the plasma or serum concentrations of gemfibrozil following a single 2 x 300 mg or 1 x 600 mg dose of the test formulation with those observed for the reference formulation Lopid (Parke-Davis) in the same strength and dosage form as the test product under fasting conditions.

*Design:*  The study design is a single dose, two treatment, two period, two sequence crossover with a washout period of at least two weeks.  Subjects should be randomly assigned to the two possible dosing sequences.

*Facilities:*  The clinical and analytical sites for the study should be given along with the names, titles and the curriculum vitae of the medical, scientific and analytical directors.  The starting and ending dates for each clinical study period should be stated.  The study protocols should be approved by an institutional review board, and informed consent forms should be signed by all participants.

*Subjects*:  A minimum of 24 subjects should be used.  It

is the sponsor's responsibility to use enough volunteers to ensure adequate statistical results.

The subjects should be healthy male volunteers between 18 and 50 years of age and within $\pm$ 10% of the ideal weight for their height and body frame according to the Metropolitan Insurance Company Bulletin, 1983. All subjects should be given a physical examination and appropriate laboratory tests 4 weeks prior to the initiation of the study. These should be repeated at the end of the study.

*Exclusion Criteria*: Subjects should be excluded from the study using the following criteria and any other criteria deemed necessary by the medical director of the study:

1.     History of alcoholism or drug abuse.

2.     History of any of the following diseases or conditions: clinically significant endocrine, hematological, gastrointestinal, or hepatic abnormalities, or deteriorating renal function that could interfere with the drug's absorption, biotransformation, or elimination.

3.     Clinical laboratory test values falling outside the normal range which are confirmed on reexamination if deemed clinically significant.

4.     Tobacco use in any form.

5.     Blood donation within 30 days prior to the start of the study.

6.     Ingestion of any investigational drug within 30 days before the start of the study.

7.     Known hypersensitivity or allergy to gemfibrozil or any other related compound.

*Restrictions*:

1.     Water will be allowed  *ad libitum* except for two hours before and after drug administration.

2.   Subjects should be served standardized meals no
     less than 4 hours after drug administration.  Only
     standardized meals and beverages at specified
     times will be allowed during the study.

3.   No alcohol or xanthine-containing foods or
     beverages should be consumed for 48 hours prior to
     each study period and until after the last blood
     sample is collected.

4.   No drugs, including OTC preparations, may be taken
     within 2 weeks of the start of the study or during
     any of the study phases.

*Procedures*:  After an overnight (at least 10 hours)
fast, subjects should receive one of the following
treatments with 240 ml of water:

Treatment A:    2 x 300 mg capsules or 1 x 600 mg tablet
                of gemfibrozil or

Treatment B:    2 x 300 mg capsules or 1 x 600 mg tablet
                of the reference product Lopid [R] (Parke-
                Davis).

The test product should be taken from a lot of at least
100,000 finished dosage units.  The lot numbers of both
test and reference products and the expiration date for
the reference product should be stated.  The potency of
the reference product should not differ from that of
the test product by more than ±5%.  The sponsor should
include a statement on the composition of the test
product and, if possible, a side-by-side comparison of
the compositions of test and reference products.

*Blood sampling*:  Blood samples should be drawn at 0,
0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 14
hours after the administration of the drug.
Serum/plasma should be separated and immediately stored
at -20°C in light resistant containers.

*Analytical methods*:  The analysis  of gemfibrozil
should be undertaken by a suitable method which is
sensitive, specific, linear and reproducible.  Both
gas-liquid chromatographic and high performance liquid
chromatographic methods have been used for the
determination of gemfibrozil in plasma/serum (17-19).

Stability of the samples under frozen conditions, at room temperature, and during freeze-thaw cycles, if appropriate, should be determined (20).

*Pharmacokinetic Analysis*:  From plasma drug concentration-time data, the sponsor should obtain the following pharmacokinetic parameters:

1.  $AUC_{0-t}$, calculated by the trapezoidal rule, where t is the last measurable time point.

2.  $AUC_{0-\infty}$, where $AUC_{0-\infty} = AUC_t + C_t/(\lambda_z)$, $C_t$ is the last measurable drug concentration and $\lambda_z$ is the terminal elimination rate constant.

3.  The terminal phase elimination rate constant ($\lambda_z$) is calculated using an appropriate pharmacokinetic method.

4.  Peak drug concentration ($C_{max}$) and the time to peak drug concentration ($T_{max}$) are obtained directly from the data without interpolation.

*Statistical Analysis*:   The sponsor should perform the following tests:

1.  Analysis of variance (ANOVA) appropriate for a crossover design on the pharmacokinetic parameters $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ using General Linear Models (GLM) procedure of SAS (21) or an equivalent program should be performed.  The statistical model should include terms describing the effects attributable to sequence, subject(sequence), period, and treatment.  The sequence effect should be tested using the between-subject main effect [subj(seq)] as an error term.  All other main effects should be tested against the residual error (error mean square) from the ANOVA.

2.  The ESTIMATE statement in SAS should be used to obtain estimates for the adjusted differences between treatment means and the error associated with these differences.

3.  The LSMEANS statement should be used to calculate least-square means for treatments.

4.  The two one-sided tests procedure should be used

to calculate 90% confidence intervals for the mean difference for AUC and $C_{max}$, which should generally be within $\pm$ 20% of the corresponding reference mean.

*Adverse Reactions*:  The sponsor should report all adverse reactions that occurred during the study with regard to the nature, onset, duration, frequency, severity, type of treatment during which the reaction occurred and the suspected relation to the drug treatment.

## III. IN VITRO STUDIES

A.   Dissolution testing

Dissolution testing should be conducted on 12 dosage units of the test and reference products from lots used in the *in vivo* bioequivalence study.  The following procedure should be used.

| | |
|---|---|
| Apparatus: | USP XXII Apparatus 2 (paddle) |
| Speed: | 50 rpm |
| Medium: | 0.2 M Phosphate Buffer, pH 7.5 at 37 °C |
| Volume: | 900 mL |
| Sampling Time: | 15, 30, 45 and 60 minutes |
| Assay: | UV at 276 nm |
| Specification: | Not less than 80% of the drug in the dosage form is dissolved in 45 minutes |

For dissolution testing the sponsor should include the following:

1.   Comparative dissolution profiles for the test and reference products at 15, 30, 45, and 60 minutes.

2.   For each time interval, the percent dissolution for each dosage unit should be tested.

3.   For each time interval, the mean percent dissolved, the range of percent dissolution for the 12 dosage units, and the coefficient of variation should be provided.

4.   The validated analytical method used.

5.   The lot numbers for the test and reference products.

6.    Expiration date for the reference product.

The test drug product used in the *in vivo* bioequivalence study and *in vitro* dissolution testing should be from the same production batch.

B.    Content uniformity test

Content uniformity (CU) data for 10 capsules or 10 tablets from the lot used in the *in vivo* studies should be submitted along with the *in vitro* dissolution testing data.

C.    Potency determination

Prior to initiation of the bioequivalence study, the applicant should determine the potency of the lots of the test and reference drug products to be used in the study. It is recommended that the applicant ensure that the potency of the reference product lot used in the bioequivalence study is within ± 5% of that of the test drug product.  The data on potency should be submitted along with the dissolution data.

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